

A Study of the Steric Hindrance Effect
of Various Substituent Groups in
the Ortho Position to the Car-
boxyl on the Reaction which
Takes Place when Para-
sulphamidobenzoic Acids
are Heated to 220°

DISSERTATION

SUBMITTED TO THE BOARD OF UNIVERSITY STUDIES OF
THE JOHNS HOPKINS UNIVERSITY IN CONFORMITY
WITH THE REQUIREMENT FOR THE DE-
GREE OF DOCTOR OF PHILOSOPHY

BY

JOHN WILLIAM NOWELL

BALTIMORE, JUNE, 1912

EASTON, PA.:

ESCHENBACH PRINTING COMPANY

1912

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ACKNOWLEDGMENT

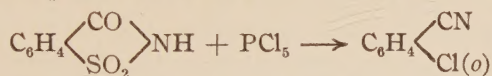
This investigation was carried out at the suggestion of President Remsen under the guidance of Dr. Rouiller, for whose timely suggestions and otherwise helpful instruction I wish to express my grateful appreciation. I also wish to thank President Remsen, Professors Morse and Jones, and Associate Professors Acree, Renouf, Lovelace and Swartz for very valuable instruction received from them.

A Study of the Steric Hindrance Effect of Various Substituent Groups in the Ortho Position to the Carboxyl on the Reaction which Takes Place when Parasulpham- idobenzoic Acids are Heated to 220°

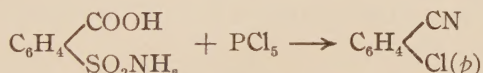
INTRODUCTION

Inasmuch as this dissertation deals with a problem which was begun by Remsen and Hartman in 1894 but, for several reasons, has been discontinued since 1901, except the work of Dr. Rouiller,¹ it seems to the writer that a brief account of the development of this problem should be given that the reader may be able to see the work as a whole and thereby be better enabled to understand the purpose of the present investigation.

In 1889, Remsen and Dohme² showed that *o*-chlorobenzonitrile was formed by the action of phosphorus pentachloride on benzoic sulphinide as follows:



They also mention the fact that a similar reaction takes place on treating *p*-sulphamidobenzoic acid with phosphorus pentachloride:



But the nitrogen of *p*-sulphamidobenzoic acid is combined with sulphur and not with carbon and in view of the fact that the substituting groups are farther apart in space in this case than in that of saccharin, the migration of the nitrogen atom under such conditions makes the reaction a very remarkable one.

In 1894, Hartman³ took up the question of how this fundamental change takes place and was able to show that when *p*-sulphamidobenzoic acid is heated to 285° it is converted

¹ Am. Chem. J., **47**, 475.

² *Ibid.*, **11**, 347.

³ Diss., Johns Hopkins Univ., 1894; Am. Chem. J., **18**, 151.

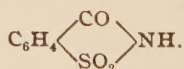
entirely into a soluble compound, the acid ammonium salt of *p*-sulphobenzoic acid, but if heated at 235° till melted, the product is only partially soluble.

The following year Muckenfuss¹ took up the problem in the hope that he might obtain additional evidence of the shifting of the nitrogen in *p*-sulphamidobenzoic acid and isolate intermediate products if possible. From the products obtained by heating *p*-sulphamidobenzoic acid eight hours at 220°, he was able to isolate the following substances:

1. The acid ammonium salt of *p*-sulphobenzoic acid.
2. Free *p*-sulphobenzoic acid.
3. An infusible and insoluble substance which he called the "Infusible Diamide."
4. An acid which he called "Iso-*p*-sulphaminebenzoic acid."

Muckenfuss tried to split off half of the nitrogen from the "infusible diamide" to see if the salt of an acid isomeric with *p*-sulphamidobenzoic acid would be formed but all his attempts were unsuccessful.

In 1897 Stoddard² succeeded in doing this by boiling the "infusible diamide" with magnesium hydroxide but further efforts to clear up the constitution of the "infusible diamide" yielded no results. By analyzing several salts of the "iso acid" of Muckenfuss, Stoddard was able to show fairly conclusively that this substance is not isomeric with *p*-sulphamidobenzoic acid but rather corresponds to the anhydride of *p*-sulphamidobenzoic acid,



Chamberlain's³ work was chiefly a confirmation of that of Stoddard, for he was unable to throw any further light on the nature of the "infusible diamide."

Nakaseko,⁴ working with *m*-sulphamidobenzoic acid, was able, by heating it at 220° for several hours, to obtain products analogous to those obtained from the para compound except that no analogue of the "iso acid" of Muckenfuss or sulphinide

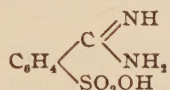
¹ Diss., Johns Hopkins Univ., 1895; Am. Chem. J., **18**, 349.

² Diss., Johns Hopkins Univ., 1897; Am. Chem. J., **47**, 1.

³ Diss., Johns Hopkins Univ., 1899; Am. Chem. J., **47**, 318.

⁴ *Ibid.*, 429.

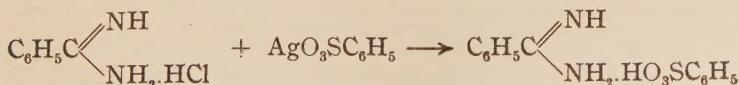
of Stoddard was found. To Nakaseko must be given the credit of being the first worker to suggest an amidine structure for the "infusible diamide." In his dissertation, page 19, he says: "As to the nature of the isomerism of this new compound with ordinary *m*-sulphobenzoic diamide, I am in utter darkness. The tendency of nitrogen atoms in organic compounds to combine with carbon atoms at higher temperatures makes the following constitutional formula for this new substance probable:



The perfectly neutral reaction, the insolubility and infusibility of the substance, seem to point to the formation of an inner salt and the easy splitting off of both nitrogen atoms does not justify the assumption of the existence of the sulphamido group in the new compound."

Waters¹ studied the effect of heat on *p*-sulphamido-*m*-toluic acid in order to find out what influence a methyl group in the ortho position to the sulphamido group would exert. He was able to isolate compounds analogous to those obtained in the case of *p*- and *m*-sulphamidobenzoic acids but the question of the constitution of the "infusible diamide" was still left unanswered. Simmons² took up the work at this point in 1901 for the purpose of clearing up the structure of the "infusible diamide" but was unable to obtain direct proof, though all his results pointed to the probability that Nakaseko's formula was the correct one, since by it only could his reactions be satisfactorily explained.

In 1906 Robinson³ prepared benzamidine benzenesulphonate by treating benzamidine hydrochloride with silver benzenesulphonate in 95 per cent. alcohol according to the following reaction:



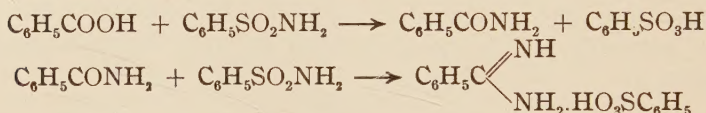
¹ Diss., Johns Hopkins Univ., 1899; Am. Chem. J., **47**, 333.

² Diss., Johns Hopkins Univ., 1901.

³ Diss., Johns Hopkins Univ., 1906.

This benzamidine benzenesulphonate was found to be a well defined crystalline substance, fairly soluble in cold water and melting at 174° .

Dr. Rouiller¹ has prepared benzamidine benzenesulphonate by heating together at 220° benzoic acid and benzenesulphonamide according to the following reaction:



the resulting compound being identical with the benzamidine benzenesulphonate prepared by Robinson. Towards alkalis, magnesium hydroxide and acids, this substance behaves like the "infusible diamide." This latter substance was prepared in an entirely analogous manner by heating *p*-sulphobenzoic acid with benzenesulphonamide. The above facts seem to establish fairly conclusively the amidine structure of the "infusible diamide."

For the last two years, Dr. Rouiller has been studying the reaction between various organic acids and benzenesulphonamide at 220° for the purpose of determining the amount of amidine formation and has reached the conclusion that the reaction, though applicable to a number of cases, does not seem to be a general one. The fact that *m*- and *p*-nitrobenzoic acids easily give the corresponding amidines while the ortho acid does not² seems to show that steric hindrance plays a part in the reaction.

At the suggestion of President Remsen, the present investigation was undertaken to find out what effect substituent groups in the ortho position to the carboxyl in *p*-sulphamido

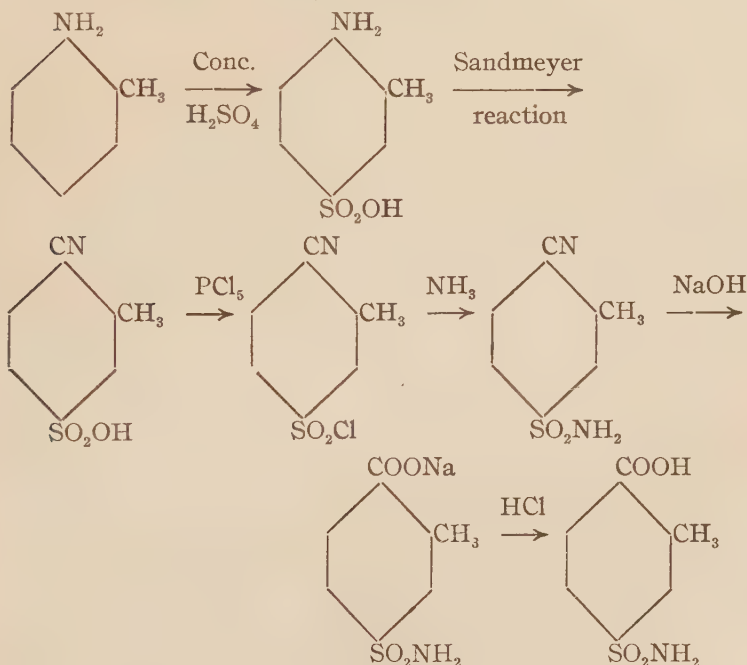
¹ Am. Chem. J., **47**, 475.

² Am. Chem. J., **47**, 490. In the case of the *o*-acid, no attempt was made to isolate an amidine, as the product, on distillation with magnesium and sodium hydroxides, successively, lost, as ammonia, 61.3 per cent. of the nitrogen originally present as benzenesulphonamide with the magnesium hydroxide, and only 3.5 per cent. with the sodium hydroxide, whereas any amidine, if formed, should lose equal amounts of nitrogen with each reagent. It was concluded, therefore, that practically nothing but an ammonium salt was formed. It may be, however, that the nitro group in the *o*-position prevented the hydrolysis of any amidine which might have been formed. The experiment will be repeated on a larger scale and an attempt made to isolate all the products formed.—C. A. R.

acids would exert on the general reaction which takes place on heating *p*-sulphamido acids to 220°. For this purpose *p*-sulphamido-*o*-toluic acid was first selected.

Preparation of Material

On looking into the literature, it was found that Jacobsen¹ had prepared *p*-sulphamido-*o*-toluic acid by oxidizing *p*-sulphamido-*o*-xylene, but in view of the fact that *o*-xylene is rather costly and difficult to obtain in sufficient quantities, the following method for preparing *p*-sulphamido-*o*-toluic acid was tried and found to be very satisfactory:



a. Preparation of p-Sulpho-o-toluidine.—Five hundred grams of *o*-toluidine, which had been freshly distilled to remove the coloring matter which always accompanies the commercial product, were treated with five hundred grams of concentrated sulphuric acid according to the method of Neville and

¹ Ber. d. chem. Ges., 11, 22; 14, 39.

Winther¹ as follows: The mixture of *o*-toluidine and sulphuric acid was heated in an open balloon flask, placed in a paraffin bath which was kept at 220°. The contents of the flask are frequently stirred and the heating continued till the whole mass becomes solid, which usually requires from four to five hours. The solid bonelike mass is extracted with boiling water from which, on cooling, the *p*-sulpho-*o*-toluidine crystallizes out in long slender needles. Yield, 70–80 per cent. of the theoretical.

b. Preparation of p-Sulpho-o-tolunitrile.—This was prepared from the *p*-sulpho-*o*-toluidine by the Sandmeyer reaction according to the directions given in Gattermann's "Praxis des organischen Chemikers." The diazotized product precipitated out of solution, so I filtered it off and added it, suspended in water, to the cuprous cyanide solution. When the solution had cooled, I added hydrochloric acid and a dirty, yellowish gray precipitate came down, consisting chiefly of copper salts. This clayey looking precipitate was filtered off and the solution concentrated to about one-third its volume. On cooling, the potassium salt of *p*-sulpho-*o*-tolunitrile crystallized out in long silky needles and from more concentrated solutions in rosettes with needles radiating from the center. The last portions were extracted with boiling alcohol to separate the nitrile from inorganic salts. Yield, about 90 per cent. of the theoretical.

c. Preparation of the Chloride of p-Sulpho-o-tolunitrile.—The above potassium salt was treated with its own weight of phosphorus pentachloride (slightly more than one molecule), and rubbed up in a mortar, when a vigorous reaction took place and the whole mass melted to a thick, brownish yellow liquid. The product was heated for some time on the water bath to drive off all fumes and to complete the reaction. When cool, it was washed with ice water, generally about six or seven times, to take out all inorganic salts. The product crystallized from ligroin in beautiful, colorless crystals, mostly diamond-shaped or rather elongated diamonds with stria-

¹ Ber. d. chem. Ges., **13**, 1940.

tions on the faces, melting at 52° .5– 53° . Yield, about 50 per cent.

d. Preparation of p-Sulphamido-o-tolunitrile.—The crude acid chloride, after being washed about six times with ice water, was treated with concentrated ammonia. When stirred vigorously, a very noticeable reaction set in and in a short time all the acid chloride dissolved, leaving a clear, brownish yellow solution. On concentrating to a small volume, which eliminated the excess of ammonia, the *p*-sulphamido-*o*-tolunitrile came down in brownish fluffy crystals which, after boiling with charcoal, separated in long crystals with rough edges somewhat like saw teeth. After several recrystallizations, the crystals still had a slight yellowish color but the melting point was constant at 159° – 160° . Yield, about 75 per cent.

e. Preparation of p-Sulphamido-o-toluic Acid.—The *p*-sulphamido-*o*-tolunitrile was digested for six hours with an excess of caustic soda. There was a copious evolution of ammonia. When the reaction was complete, the solution was cooled and acidified with hydrochloric acid, when the whole mass almost solidified, so fine and silky were the crystals. After five crystallizations, the acid came out in beautiful colorless, silky needles, melting at 211° . From five hundred grams of *o*-toluidine I obtained one hundred and fifty grams of the crystallized acid.

Analyses:

0.3643 gram heated two hours at 109° lost 0.0004 gram.

0.3643 gram heated two hours at 150° gained 0.0013 gram.

0.5057 gram heated two hours at 145° gained 0.0001 gram.

From the above results it is evident that *p*-sulphamido-*o*-toluic acid contains no water of crystallization.

0.6066 gram of the acid required 28.25 cc. of 0.1 N alkali to neutralize it.

0.5741 gram of the acid required 26.72 cc. of 0.1 N alkali to neutralize it.

	Calculated for $\text{CH}_3\text{C}_6\text{H}_3(\text{SO}_2\text{NH}_2)\text{COOH}$	I	Found II
Molecular weight	215.15	214.72	214.85

0.1994 gram gave 0.2105 gram BaSO_4 (Liebig).

0.2270 gram gave 0.2485 gram BaSO_4 (Liebig).

	Calculated for $\text{CH}_3\text{C}_6\text{H}_3(\text{SO}_2\text{NH}_2)\text{COOH}$	I	Found	II
S	14.9	14.5		15.03

Potassium Salt.—This salt was prepared by neutralizing 5 grams of *p*-sulphamido-*o*-toluic acid with potassium hydroxide and evaporating to crystallization, when it came out in beautiful colorless, glasslike crystals. It has been described by Jacobsen¹ as glassy prisms of rhombohedral habit.

Analyses:

0.6362 gram lost 0.0222 gram of water at 150° .

0.6002 gram lost 0.0207 gram of water at 150° .

0.6140 gram gave 0.2057 gram K_2SO_4 .

0.5795 gram gave 0.1938 gram K_2SO_4 .

	Calculated for $\text{CH}_3\text{C}_6\text{H}_3(\text{SO}_2\text{NH}_2)\text{COOK} + 0.5\text{H}_2\text{O}$	I	Found	II
K	14.89	15.03		15.00
H_2O	3.43	3.44		3.48

Ammonium Salt.—By treating *p*-sulphamido-*o*-toluic acid with ammonia, a substance was obtained which crystallized easily from concentrated water solutions in crystals like elongated diamonds melting at 169° – 172° . In no case was the melting point sharp at all.

0.4224 gram gave with $\text{Mg}(\text{OH})_2$ ammonia equivalent to 16.9 cc. 0.1 cc. 0.1 N acid.

0.5246 gram lost 0.041 gram at 120°

	Calculated for $\text{CH}_3\text{C}_6\text{H}_3(\text{SO}_2\text{NH}_2)\text{COONH}_4 \cdot \text{H}_2\text{O}$	Found
0.5 N	5.60	5.60
H_2O	7.20	7.81

Preparation of Acid Ammonium p-Sulpho-o-toluate.—Following Waters' method² for preparing his acid ammonium salt, ten grams of *p*-sulphamido-*o*-toluic acid were mixed in a sealed tube with 20 cc. of concentrated hydrochloric acid and heated at 200° for ten hours. On removal of the tube from

¹ Ber. d. chem. Ges., **14**, 39.

² Diss., Johns Hopkins Univ., 1899, p. 28. Am. Chem. J., **47**, 349.

the furnace; small prismatic crystals were observed all through the mass. The contents of the tube were dissolved in water and on concentrating the solution, prismatic crystals melting at 285° – 288° were obtained. After about six crystallizations from water, I obtained crystals having a melting point of 288° – 289° . The salt was identical with that obtained by heating the sulphamido acid at 220° (see p. 23).

Attempt to Prepare the Diammonium Salt of p-Sulpho-o-toluic Acid.—I hydrolyzed potassium *p*-sulpho-o-tolunitrile with caustic potash, then saturated an alcoholic solution of the resulting salt with hydrochloric acid gas, when the potassium chloride was precipitated out and the filtered solution evaporated to dryness to remove the hydrochloric acid. The free *p*-sulpho-o-toluic acid was now neutralized with ammonia, but I was never able to get the diammonium salt out pure enough for analysis, because it is hydrolyzed so easily. By recrystallizing from acetone, I obtained shiny grains melting at 211° – 215° . From water it came down as long, slender prisms at first, about half of which melted at 215° , and the remainder at 269° – 271° . On standing overnight the bottom of the beaker became covered with short, thick prisms, identical in appearance with the acid ammonium salt and which showed no signs of melting till 275° was reached. The solution had also become distinctly acid, proving conclusively that the diammonium salt was being hydrolyzed to the acid ammonium salt. No analysis was made, as crystals of a definite melting point were not obtained. See also page 22 for the analogous behavior of the solution of the product obtained by heating *p*-sulphamido-o-toluic acid and then neutralizing with ammonia.

Waters¹ encountered the same difficulty in trying to prepare the diammonium salt of *p*-sulpho-*m*-toluic acid by precipitating exactly the barium from a solution of the sulphotoluic acid by means of ammonium sulphate. Instead of obtaining the diammonium salt, he obtained only the acid ammonium salt. He says that "this surprising result could be due only to a loss of ammonia on evaporating the solution."

¹ Diss., Johns Hopkins Univ., 1899, p. 28.

Preparation of the Acid Barium p-Sulpho-o-toluate.—Thirty grams of the product obtained by heating *p*-sulphamido-*o*-toluic acid (see page 21) were dissolved in water and divided into two equal parts. One part was just neutralized with barium hydroxide and then added to the other half of the solution. On standing overnight a grayish powder came down and, over it, some clusters of needles very soluble in water. When boiled with charcoal and recrystallized from water, the substance came out in small, shiny, silky plates which showed no signs of melting up to 300°. After several recrystallizations from water, I obtained pure white needles arranged mostly in rosettes which, when dried, had a leafy, glassy appearance.

Analyses:

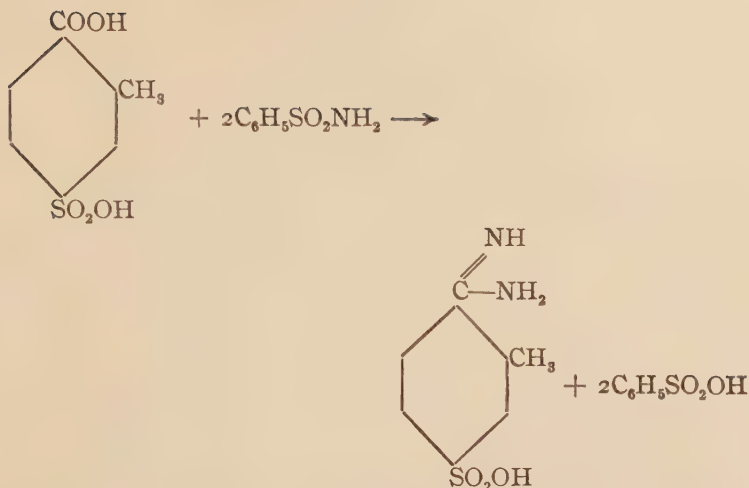
0.4188 gram gave 0.1635 gram BaSO₄ (Liebig).

0.4256 gram gave 0.1653 gram BaSO₄ (Liebig).

0.3091 gram lost 0.0182 gram when heated 8 hours at 175°.

	Calculated for $\left(\text{CH}_3\text{C}_6\text{H}_3 \begin{array}{l} \nearrow \text{COOH} \\ \searrow \text{SO}_3 \end{array} \right)_2 \text{Ba} \cdot 2\text{H}_2\text{O}$	Found
Ba	22.77	22.85–22.97
H ₂ O	5.96	5.88

Attempt to Prepare p-Sulpho-o-toluamidine.—*p*-Sulpho-*o*-toluic acid was made by digesting *p*-sulpho-*o*-tolunitrile with an excess of barium hydroxide, till hydrolysis was complete, then the barium was exactly precipitated with sulphuric acid and the filtered solution evaporated to dryness, when the free sulphotoluic acid was obtained as a white amorphous powder. By heating *p*-sulpho-*o*-toluic acid with benzenesulphonamide, I hoped to obtain the amidine by the following reaction:



Twelve grams of the acid and eighteen grams of benzenesulphonamide were thoroughly mixed and heated in a sealed tube for two and one-half hours at 225° . The mixture melted to a dark brown mass which was readily soluble in cold water except for a trace of carbonaceous matter. The solution was extracted three times with 25 cc. portions of ether and on evaporating the ether extract, there remained a few oily drops which had a distinct nitrile odor and gave off ammonia with sodium hydroxide. The water solution was just neutralized with barium hydroxide and evaporated to dryness. I then extracted the dry residue with absolute alcohol that I might separate the barium salts from the products soluble in alcohol.

Alcoholic Extract.—When evaporated to crystallization, the alcoholic solution deposited an amorphous powder melting at 245° – 275° . I was never able to get any characteristic crystals. After three recrystallizations, the substance melted at 270° – 290° and gave off about twice as much ammonia with magnesium hydroxide as with sodium hydroxide, though the amount of ammonia was far too small for the acid ammonium salt.

0.3405 gram gave with $\text{Mg}(\text{OH})_2$ ammonia equal to 2.7 cc. 0.1 N acid and with NaOH ammonia equal to 1.15 cc. 0.1 N acid.

	Calculated for	
	$\text{CH}_3\text{C}_6\text{H}_3 \begin{cases} \text{COOH} \\ \text{SO}_2\text{NH}_4 \end{cases}$	
N	6.01	Found 1.58

Substance Insoluble in Alcohol.—The portion insoluble in alcohol was treated with ammonium sulphate till the barium was just precipitated, the barium sulphate filtered off and the solution evaporated to dryness. The dried residue was then dissolved in alcohol and precipitated with ether, by which method I obtained an amorphous powder melting at 240° – 252° . The ammonia liberated from this substance by boiling 0.250 gram with magnesium hydroxide neutralized 18.6 cc. 0.1 N acid and that set free by caustic soda neutralized only 0.45 cc. 0.1 N acid, so it is evident that the nitrogen is present in the form of ammonium salts, very probably a mixture of $\text{C}_6\text{H}_5\text{SO}_3\text{NH}_4$ and $\text{CH}_3\text{C}_6\text{H}_3 \begin{cases} \text{COONH}_4 \\ \text{SO}_2\text{ONH}_4 \end{cases}$. Not a trace of amidine was found.

Attempts to Prepare Carbamido-o-toluene-p-sulphonic Acid.—The method of Radziszewski¹ for obtaining amides from nitriles by the action of hydrogen peroxide was first tried. Potassium *p*-sulpho-*o*-tolunitrile was treated with a slightly alkaline solution of hydrogen peroxide and warmed on the water bath at 40° till the evolution of gas ceased. On concentration, the solution deposited only an amorphous powder which, when treated with ammonia, gave a substance melting at 185° – 195° , chiefly the diammonium salt of *p*-sulpho-*o*-toluic acid, showing that the nitrile group was saponified completely to the carboxyl group, yielding only *p*-sulpho-*o*-toluic acid.

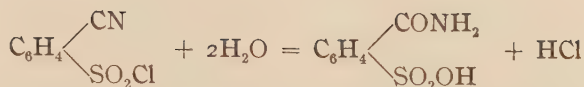
Simmons² found the same thing in the case of *p*-sulphobenzonitrile, for when he treated the nitrile with alkaline hydrogen peroxide, he got only *p*-sulphobenzoic acid.

I next tried the method of Jesurun,³ who obtained *p*-sulphobenzamide by the following reaction:

¹ Ber. d. chem. Ges., **18**, 355.

² Diss., Johns Hopkins University, 1901.

³ Ber. d. chem. Ges., **26**, 2289.



the reaction taking place in a sealed tube at 95° – 100° . Five grams of potassium *p*-sulpho-*o*-tolunitrile with 5 cc. of 0.1 N sulphuric acid were heated in a sealed tube for five hours at 100° . When the tube was opened and the contents evaporated to crystallization, I obtained the original nitrile unchanged.

The successful method for preparing the carbamido-*o*-toluene-*p*-sulphonic acid was finally discovered accidentally. All attempts to prepare the free sulphotolunitrile from the potassium salt by dissolving it in water and acidifying with hydrochloric acid having failed, I dissolved the salt in absolute alcohol and saturated the solution with dry hydrogen chloride gas, hoping thus to throw out the potassium as potassium chloride and obtain the free *p*-sulpho-*o*-tolunitrile. During the process the temperature was allowed to rise almost to the boiling point of the alcohol. The potassium chloride was filtered off and the alcoholic solution evaporated to a small volume but nothing would crystallize out, so I evaporated the solution to dryness and heated the residues on the water bath till all the hydrochloric acid was expelled. The residue was strongly acid. It was neutralized with ammonia and on crystallization I obtained beautiful, long, prismatic crystals melting at 276° – 278° .

Analysis:

0.3081 gram gave with $\text{Mg}(\text{OH})_2$ ammonia equivalent to 13.1 cc. 0.1 N acid, and with NaOH ammonia equivalent to 13.6 cc. 0.1 N acid.

	Calculated for		Found	
	$\text{CH}_3\text{C}_6\text{H}_3(\text{CN})\text{SO}_2\text{NH}_4$	$\text{CH}_3\text{C}_6\text{H}_3(\text{CONH}_2)\text{SO}_2\text{NH}_4$	$\text{Mg}(\text{OH})_2$	NaOH
0.5 N	6.54	6.03	5.95	6.18

Preparation of the Barium Salt—Another portion of the acid residue was neutralized with barium hydroxide, and after several crystallizations I was able to get out the barium salt reasonably pure.

Analysis:

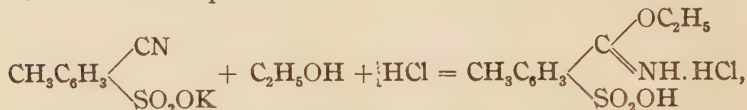
0.5183 gram lost 0.0283 gram at 200° .

0.6933 gram gave 0.2687 gram BaSO_4 .

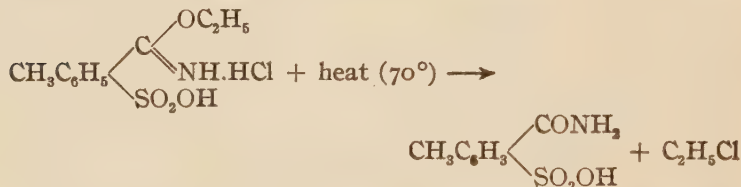
0.3224 gram gave 0.1250 gram BaSO_4 .

	Calculated for [CH ₃ C ₆ H ₃ (CONH ₂)SO ₂] ₂ Ba.2H ₂ O	I	Found II
Ba	22.84	22.80	22.81
H ₂ O	5.99	5.46	...

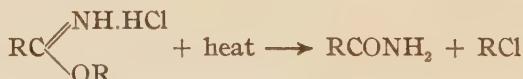
From the above analyses of the ammonium and barium salts of this acid it seems very probable that the following reaction has taken place:



and that the imido ester at the temperature of the reaction breaks up as follows:



Pinner¹ says that imido esters in the solid state break down as follows when heated:



so to satisfy myself that the same reaction takes place in alcohol when the temperature is allowed to rise nearly to the boiling point, I tested benzonitrile in the same way as the sulphotolunitrile above and, though I obtained some ammonium chloride, I also was able to isolate quite a considerable amount of benzamide. The ammonium chloride, being insoluble in absolute alcohol, was filtered off and on concentrating the alcoholic solution a white crystalline substance came out having a melting point of 128°, identical with that of benzamide, and when mixed with benzamide the melting point remained constant. Judging from the analyses of the two salts and the analogous experiment with benzonitrile, it is pretty conclusively shown that by treating an alcoholic solution of potassium *p*-sulpho-*o*-tolunitrile with hydrochloric acid gas, there

¹ Die Imido-aether, p. 5.

is formed, not *p*-sulpho-*o*-tolunitrile, but 1-carbamido-2-methylbenzene-4-sulphonic acid.

Determination of the Most Suitable Conditions for Heating p-Sulphamido-o-toluic Acid.—Since *p*-sulphamido-*o*-toluic acid does not lose any of its nitrogen when boiled with either magnesium hydroxide or caustic soda while amidines lose one atom of nitrogen as ammonia when boiled with magnesium hydroxide and another atom when boiled with caustic soda, it was thought that by boiling successively with these two reagents the product obtained by heating the acid at various temperatures and different lengths of time some indication might be obtained as to the extent of any reaction which might have taken place similar to that observed in the case of *m*- and *p*-sulphamido-benzoic and *p*-sulphamido-*m*-toluic acids, and that in this way the most favorable conditions for heating the acid in larger quantities might be determined.

I. 0.4850 gram heated in a sealed tube two hours at 220° gave with $\text{Mg}(\text{OH})_2$ 48.59 per cent. nitrogen; with NaOH 42.96 per cent. nitrogen.

II. 0.4484 gram heated in a sealed tube four hours at 220° gave with $\text{Mg}(\text{OH})_2$ 47.71 per cent. nitrogen; with NaOH 40.44 per cent. nitrogen.

III. 0.4999 gram heated in a sealed tube six hours at 240° gave with $\text{Mg}(\text{OH})_2$ 56.80 per cent. nitrogen; with NaOH 23.26 per cent. nitrogen.

From the above tests it appears that two hours' heating at 220° is the most favorable condition for preparing the melt of *p*-sulphamido-*o*-toluic acid.

Preparation of the Melt.—The heating was carried out in a large paraffin bath, the temperature of which could be kept constant to within 2°–3° for a long time.

Test tubes, each containing ten grams of acid and closed loosely with a cork stopper, were heated for two hours at 220° and then allowed to cool in the air. Unlike the melt from *p*-sulphamido-*m*-toluic acid, that from *p*-sulphamido-*o*-toluic acid showed no signs of deliquescence at all. When cool the tubes were broken and the melt removed. The melt was now a dark, brown, brittle mass, very shiny and resembling sealing

wax somewhat. When the tubes were opened there was always a distinct nitrile odor and around the top of each tube was observed a very small amount of a sublimate which had the same melting point as the original acid and, when mixed with the acid, still melted at the same temperature, indicating that the sublimate was unchanged *p*-sulphamido-*o*-toluic acid.

Treatment of the Melt.—The first three melts were worked with the main idea of isolating first any “infusible diamide” which might have been formed. Several portions of the melt were subjected to different methods of treatment, so it might not be out of place to give each method separately.

I. Twenty grams of the melt were ground up in a mortar and extracted with cold water until all the substance had dissolved, giving a reddish brown solution, slightly milky in appearance. Unlike the melts of previous workers, the melt of *p*-sulphamido-*o*-toluic acid was completely soluble in a relatively small quantity of cold water. On standing overnight, a very small amount of a flocculent substance settled out which was soluble in alkalis and reprecipitated by acids. The amount of the substance was far too small for analysis and I never again obtained any of the substance from the other melts.

The clear filtrate was now evaporated to dryness and extracted with acetone.

a. Acetone Extract.—Only a very small portion of the melt was soluble in acetone. On evaporating off the acetone, small, light yellow nodules, having a melting point of 192° – 200° , settled to the bottom. When recrystallized from water, it melted at 165° – 170° . The amount of substance was too small to purify for analysis.

b. Substance Insoluble in Acetone.—The greater portion of the melt was insoluble in acetone, so it was crystallized several times from water, when short, prismatic needles were formed, some arranging themselves as rosettes and some as crosses. They melted at 285° – 288° , which is the same as the melting point of acid ammonium *p*-sulpho-*o*-toluate (p. 12) and, when

mixed with the synthetic acid salt, the melting point was unchanged, proving the identity of the two substances.

II. Thirty grains of the melt was ground up in a mortar with a small amount of cold water, when all the substance went into solution readily. The water solution was extracted three times with ether and on evaporation of the ether extract a few oily drops were obtained which had a distinct nitrile odor and gave off ammonia freely with caustic soda.

The filtrate was evaporated to dryness and extracted with acetone.

a. Acetone Extract.—On evaporation of the acetone extract, nothing came down except a black tarry mass from which I was unable to isolate any definite product.

b. Substance Insoluble in Acetone.—The part insoluble in acetone was dissolved in water and just enough barium hydroxide added to neutralize the solution, which was then evaporated to dryness and the residue extracted with absolute alcohol to separate the barium salts from other salts.

1. The alcoholic extract, on concentration, gave a white amorphous powder which gave off ammonia freely with caustic soda. When recrystallized, it came down in prismatic plates and crosses melting at 242° – 248° . It was probably the impure acid ammonium salt.

2. The barium salts, insoluble in alcohol, yielded only a grayish powder which was never obtained pure enough for analysis. In another experiment (see p. 14), half of the solution of the melt in water was neutralized with barium hydroxide and added to the other half of the solution. On concentrating, acid barium *p*-sulpho-*o*-toluate crystallized out.

III. Twenty grams of the melt were next treated according to Nakaseko's¹ plan for the separation of the products of the melt. The melt was ground up in a mortar and extracted three times with ether. The ether extract yielded a few oily drops which had a distinct nitrile odor and gave off ammonia freely with caustic soda. The melt was then extracted four times with acetone, which was considerably colored by the dissolved substance.

¹ Diss., Johns Hopkins Univ., 1899. Am. Chem. J., **47**, 429.

a. The acetone extract on concentration yielded only a black tarry mass from which no definite product was isolated.

b. *Portion Insoluble in Acetone.*—The residue, which was about 95 per cent. of the whole melt, was dissolved in 50 cc. of water. The beaker was then set aside in a vacuum desiccator over sulphuric acid and allowed to stand until crystallization began. The substance came down first in the form of an amorphous powder melting at 270° – 274° , evidently impure acid ammonium salt. I tried recrystallization by the above method several times but was never able to get any distinct crystals. I then tried recrystallization from alcohol in a vacuum but was able to get no better results.

Having by the above methods been able to isolate only acid ammonium and barium sulphotoluates, I next treated the melt as follows:

IV. I heated twenty grams of *p*-sulphamido-*o*-toluic acid two hours at 223° . On cooling, the dark brown brittle mass had a distinct nitrile odor. It was dissolved in about 50 cc. of water and digested with charcoal to remove the brown color. To the now clear solution of the melt, 0.2 N ammonia was added until it was just neutral. Four hundred cc. of the ammonia was required and as 465 cc. would have been necessary to neutralize the original acid, it is evident that the acidity is practically the same after as before the heating. The neutral solution was concentrated to about one-half its volume and on standing overnight a mass of prismatic crystals came down, so thick that the beaker could be inverted without any of the solution spilling. After four crystallizations, the substance came out in shiny, needlelike, elongated prisms melting at 274° – $276^{\circ}.5$, and when mixed with some of the ammonium 1-carbamido-2-methylbenzene-4-sulphonate described above (p. 17), the melting point was unchanged, this fact, of itself, pointing to the identity of the two compounds.

Analysis of the crystals melting at 274° – $276^{\circ}.5$:

0.2686 gram boiled with $\text{Mg}(\text{OH})_2$ gave ammonia equal to 11.5 cc. 0.1 N acid; and with NaOH gave ammonia equal to 11.5 cc. 0.1 N acid.

	Calculated for $\text{CH}_3\text{C}_6\text{H}_3(\text{CONH}_2)\text{SO}_2\text{ONH}_4$	Found
With $\text{Mg}(\text{OH})_2$ N	6.035	5.99
With NaOH N	6.035	6.16
Total N	12.07	12.15

So, without a doubt, the substance in the melt that gave this ammonium salt was 1-carbamido-2-methylbenzene-4-sulphonic acid.

After filtering off the prismatic crystals described above, the mother liquor was further concentrated and the whole mass solidified without crystallizing at all. Part of it was dissolved in acetone and a substance melting at 210° – 220° , evidently the diammonium salt of *p*-sulpho-*o*-toluic acid, separated but could not be obtained in pure form. I then dissolved it in 95 per cent. alcohol and let it stand, when transparent needles or elongated prisms grouped in the form of rosettes and melting at 284° – 286° came out. Analysis of this fraction gave 8.18 per cent. nitrogen, which is between the calculated values for the acid, 6.01 per cent., and diammonium, 11.2 per cent., salts, showing very plainly that I had here a mixture of the two salts.

On standing for a day or more, the final mother liquor deposited colorless stout prisms and cubes which melted at 284° – $284^\circ.5$.

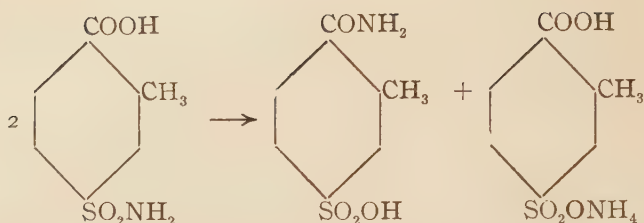
Analysis:

0.3018 gram gave with $\text{Mg}(\text{OH})_2$ ammonia equivalent to 13.00 cc. 0.1 N acid; and with NaOH only a trace.

	Calculated for $\text{CH}_3\text{C}_6\text{H}_3(\text{COOH})\text{SO}_2\text{ONH}_4$	Found
N	6.01	6.03

The final mother liquor was distinctly acid to litmus, showing that the diammonium salt is quickly hydrolyzed to the acid ammonium salt.

Having isolated only acid ammonium sulphotoluate and ammonium 1-carbamido-2-methyl-4-sulphotoluate from the melts, the course of the reaction that takes place when *p*-sulphamido-*o*-toluic acid is heated to 220° for two hours may be represented thus:



indicating that the methyl group in the ortho position to the carboxyl in *p*-sulphamido-*o*-toluic acid exercises a steric hindrance effect, arresting the reaction at an intermediate stage and preventing entirely the formation of an amidine.

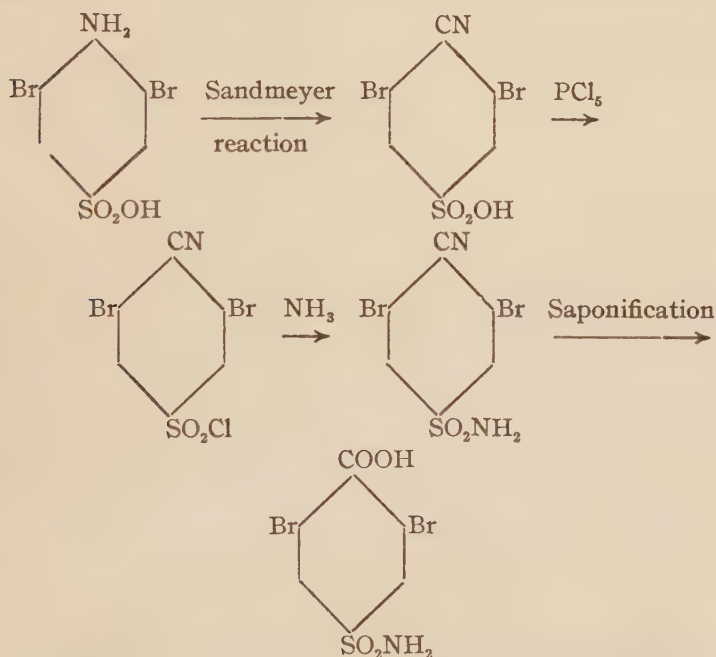
The water necessary for the formation of the acid ammonium sulphotoluate is doubtless furnished by the carbonization of a part of the acid. That the reaction proceeds essentially as represented above is indicated by the fact that the total acidity is practically unchanged and that approximately one-half of the total nitrogen is set free from the reaction product by magnesium hydroxide and the other half by sodium hydroxide (see Experiment I, p. 19).

Having tested out the effect of a methyl group in the ortho position to the carboxyl, attempts were now made to prepare other compounds with different substituent groups in the ortho position to the carboxyl group in *p*-sulphamidobenzoic acid that the relative steric hindrance effect of different substituent groups might be compared.

Attempt to Prepare 2,6-Dibromo-4-sulphamidobenzoic Acid.—Barium 2,6-dibromosulphanilate was prepared according to the directions given by Heinichen.¹ Seventy grams of sulphanilic acid were dissolved in about 2000 cc. of hot water and 84 grams of concentrated hydrochloric acid added. Into this was dropped very slowly and with vigorous shaking a cold solution of 40 cc. of bromine and 64 grams of sodium hydroxide in 600 cc. of water. During the addition of the hypobromite, a white fluffy precipitate, melting at 120°–121°, began to settle out. It was practically insoluble in water and only slightly soluble in alcohol. This product, which weighed 35 grams, was shown to be tribromoaniline. The now clear

¹ Ann. Chem. (Liebig), **253**, 269.

filtrate from the tribromoaniline was neutralized with barium carbonate and the resulting precipitate extracted with hot water. From the solution thus obtained, the barium salt of 2,6-dibromosulphanilic acid crystallized out in a fluffy mass resembling suspended asbestos. Yield of the salt, 84 grams. I hoped now by the following reactions to pass from the 2,6-dibromosulphanilic acid to 2,6-dibromo-4-sulphamidobenzoic acid:



I precipitated the barium from the barium salt with a slight excess of sulphuric acid, filtered off the barium sulphate and subjected the clear solution to the "Sandmeyer Reaction." On concentrating and cooling, a kind of jellylike, greenish mass came down which, when recrystallized from water, deposited a network of long yellow needles. The needles, however, were so very soluble in water that I made the barium salt which came out in fine shiny plates forming a fluffy mass. These were purified by recrystallization and dried for analy-

sis, but the ammonia given off by 0.8437 gram of the salt when distilled for three hours with an excess of caustic soda only neutralized 0.6 cc. of 0.1 N acid. From this, it is evident that the salt is either not a nitrile or if it is a nitrile, the two bromine groups in the ortho positions prevent saponification. In view of this fact, further attempts to prepare 2,6-dibromo-4-sulphamidobenzoic acid were abandoned for the time being.

Attempt to prepare o-Nitro-p-sulphamidobenzoic Acid.—An attempt was now made to prepare *o*-nitrosulphanilic acid according to the directions given by Nietzki and Lerch.¹ One part of acetanilide was treated with three parts of fuming sulphuric acid containing 18–20 per cent. of sulphur trioxide. Then two parts of concentrated sulphuric acid were added. The calculated amount of concentrated nitric acid, mixed with an equal volume of sulphuric acid, was dropped in slowly with constant shaking. When cooled, the mixture was poured on ice, when a broth of yellow needles should separate, the acetyl group being split off by the water. In no case, however, was I able to get any yellow needles of *o*-nitrosulphanilic acid by this method, so I turned to another method for preparing *o*-nitro-*p*-sulphamidobenzoic acid.

I began with *o*-nitrotoluene as the starting point and followed Hart's² directions for getting calcium *o*-nitrotoluene-*p*-sulphonate. One hundred and fifty grams of *o*-nitrotoluene were treated with four parts, by weight, of fuming sulphuric acid and heated on the water bath until there was no further cloudiness when dropped into water, which generally required four to five hours. This was neutralized with calcium carbonate, the calcium sulphate filtered off and the clear filtrate evaporated to a small bulk. The calcium salt was changed into the potassium salt by treating it with potassium sulphate and filtering off the calcium sulphate formed. On cooling the filtrate, the potassium salt came out in long, prismatic needles, which were dried and treated with phosphorus pentachloride. On heating the mixture on the water bath, a reaction set in and the whole mass melted to a light yellow liquid, which was washed

¹ Ber. d. chem. Ges., **21**, 3220.

² Am. Chem. J., **1**, 352.

several times with ice water and then treated with concentrated ammonia until all the substance had gone into solution. On evaporating off the excess of ammonia and decolorizing the solution with charcoal, the amide came out in fine, silky needles melting at 120° – 125° after one crystallization. By repeated crystallization from water, I obtained the amide melting at 142° – 143° , which was comparatively pure.

I thought now that by oxidizing the methyl group to carboxyl I might obtain *o*-nitro-*p*-sulphamidobenzoic acid. Two and sixteen-hundredths grams of the *p*-sulphamido-*o*-nitrotoluene were treated with 0.8 gram of potassium hydroxide to get the amide into solution, then 3.16 grams of potassium permanganate were added in small portions at a time on the water bath. There was a noticeable evolution of ammonia during the oxidation. The oxides of manganese were filtered off and the clear solution acidified with hydrochloric acid but no precipitate was formed. Barium chloride was now added to the solution and 0.18 gram of barium sulphate was obtained, showing that part of the sulphur of the amide had been oxidized to sulphuric acid. The solution was concentrated to crystallization and 1.2 grams of the original *p*-sulphamido-*o*-nitrotoluene were obtained unchanged.

Having been unable to obtain *p*-sulphamido-*o*-nitrobenzoic acid by this method, I next made *p*-sulpho-*o*-nitrobenzoic acid from calcium *o*-nitrotoluene-*p*-sulphonate, according to Hart's directions.¹

The calcium salt was oxidized on the water bath by the addition of potassium permanganate in small portions at a time, the addition of the permanganate being continued until the purple color persisted after five hours' standing on the bath, which requires generally about three to four days. The solution is now filtered from the oxides of manganese, neutralized with hydrochloric acid and evaporated to a small bulk, when hydrochloric acid is added in excess. This precipitates the acid potassium salt. This salt is easily purified by crystallization from water, when it comes out as anhydrous plates.

¹ Am. Chem. J., 1, 352.

Analysis:

0.3442 gram gave 0.104 gram K_2SO_4 .

0.2875 gram gave 0.0875 gram K_2SO_4 .

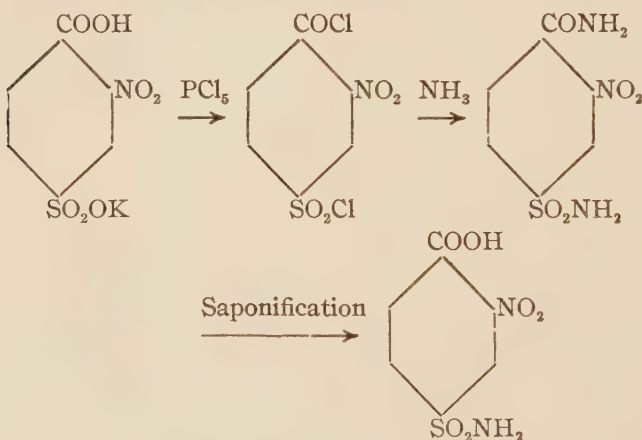
Calculated for		Found	
$O_2NC_6H_3 \begin{cases} COOH \\ SO_2OK \end{cases}$			
K	13.58	13.56	13.62

0.8672 gram required 29.87 cc. 0.1 N alkali to neutralize it.

1.1651 grams required 39.84 cc. 0.1 N alkali to neutralize it.

Calculated		Found	
Mol. wt.	285	290.3	292.4

From the acid potassium salt I hoped to obtain *o*-nitro-*p*-sulphamidobenzoic acid as follows:



I treated 68 grams of the acid potassium salt with 125 grams of phosphorus pentachloride and heated the mixture on the water bath until the whole mass liquefied. After washing about five times with 150 cc. portions of ice water, I obtained the dichloride as a thick yellow oil. This yellow oil was at first treated with concentrated ammonium hydroxide directly in order to prepare the diamide, but the reaction was so violent that I had to use dilute ammonium hydroxide. After evaporating off the excess of ammonia and heating up with charcoal,

the diamide came out in fine, silky needles, which, when re-crystallized, melted at 226° .

Analysis:

0.404 gram gave 0.3777 gram BaSO_4 (Liebig).

0.4422 gram gave 0.4276 gram BaSO_4 (Liebig).

0.3936 gram gave with NaOH ammonia equivalent to 7.7 cc. 0.1 N acid.

		Calculated for	
		$\text{NO}_2\text{C}_6\text{H}_3 \begin{cases} \text{CONH}_2 \\ \text{SO}_2\text{NH}_2 \end{cases}$	
S	$\frac{1}{3}$ N	I	Found
		II	
		12.84	13.28
		2.78	...

From the above analysis for nitrogen, it seems that the nitro group in the ortho position has prevented the saponification of the carbamido group. Five and seven-tenths grams of the diamide were now boiled with an excess of caustic soda for two days, after which the solution was neutralized with hydrochloric acid and digested with charcoal to take out the red color, which is always formed when the diamide is made alkaline. On concentrating the solution, nothing came down until it had gone nearly to dryness, when sodium chloride crystallized out. Nothing else could be isolated from the solution. From the above experiments it is evident that 1-carbamido-2-nitro-4-sulphamidobenzene cannot be saponified by the usual methods, viz., boiling with alkalis, so the method of Bouveault,¹ as modified by Gattermann,² was tried out as follows:

Twenty grams of the diamide were dissolved in a boiling solution of 50 per cent. sulphuric acid and cooled to about 60° . Then 20 grams of sodium nitrite in 30 cc. of water were gradually led into the solution of the diamide from the bottom by means of a pipette. The solution turned somewhat milky when nearly all the nitrite had been added, but on boiling it cleared up again with the evolution of a gas.

The solution was now concentrated and extracted three times with ether. On evaporating off the ether, a thick oily liquid was left which could not be made to crystallize. This

¹ Bull. soc. chim., 9, 372.

² Ber. d. chem. Ges., 32, 1118.

oily extract was dissolved in water and neutralized with barium hydroxide, when a thick precipitate came down. This precipitate was almost completely soluble in hot water, only a small amount remaining undissolved. The barium salt came down from water as an amorphous powder, which I was unable to get out pure enough for analysis because of lack of time.

It is very probable, though, that both the carbamido and sulphamido groups have been decomposed by the nitrous acid, giving *o*-nitro-*p*-sulphobenzoic acid, and the salt obtained by neutralizing the ether extract with barium hydroxide is nothing more than barium *o*-nitro-*p*-sulphobenzoate. The aqueous solution was concentrated to a very small volume, when sodium sulphate crystallized out.

At the beginning of this work, I hoped to determine the relative steric hindrance effect of various substituent groups in the ortho position to the carboxyl on the reaction which takes place when *p*-sulphamidobenzoic acids are heated to 220° but I encountered so much difficulty in the preparation of such ortho-substituted acids that I have had time to determine the influence of only one such group, viz., methyl, in *p*-sulphamido-*o*-toluic acid, and have shown that, in this case, the reaction does not proceed beyond the formation of the carbamidophosphonic acid, no trace of amidine having been detected.

BIOGRAPHICAL SKETCH

The author of this investigation was born at Tyner, North Carolina, August 15, 1883. He entered Wake Forest College, North Carolina, in 1899, receiving the A.B. degree in 1903. In 1906 he returned to Wake Forest College to pursue further studies in chemistry and received the M.A. degree in 1907. During the session 1907-1908 he was assistant in chemistry at the above college, pursuing special courses at the same time. In the fall of 1908, he entered the Johns Hopkins University where he continued as a graduate student for one year. The following year, he was instructor in chemistry at Wake Forest College and for the last two years has been doing graduate work at the Johns Hopkins University.

Subjects: Chemistry, Physical Chemistry, and Mineralogy.

